Study Population:

At baseline (2006-2010, T_0), approximately 500,000 adults aged 40 to 69 years were recruited through 22 centres in England, Scotland and Wales (16). Participants provided information on their lifestyle and medical history via electronic questionnaires and underwent physical measurements as well as blood sampling.

A subset of 20,000 participants were invited for a repeat assessment at one UK Biobank testing centre (Stockport) between August 2012 and June 2013 (first follow-up, T_1). The majority of this subset had repeat spirometry and provided repeat blood tests.

A second follow-up has been underway since 2014 (T_2). Participants were invited to repeat the baseline assessments including spirometry in one of three assessment centres (Cheadle, Reading, Newcastle).

Relevant questions for the covariates used in this study asked in UK Biobank:

"Do you smoke tobacco now?"
"About how many cigarettes do you smoke on average each day?"
"In the past, how often have you smoked tobacco?"
"How old were you when you first started smoking on most days?"
"How old were you when you last smoked on most days?"
"About how many cigarettes did you smoke on average each day?"

"In a typical WEEK, on how many days did you do 10 minutes or more of moderate physical activities like carrying light loads, cycling at normal pace? (Do not include walking)"

"About how many pieces of FRESH fruit would you eat per DAY? (Count one apple, one banana, 10 grapes etc as one piece; put '0' if you do not eat any)"

Suppl. table S1: Difference in FEV_1 and FVC (ml) and FEV_1/FVC (%) at baseline in men and women per sex-specific interquartile range increase (95% CI) in hormone measure. All participants with hormonal biomarker measurements and high quality spirometry available at baseline.

Hormonal measure	**Men** N=8,625*			**Women** N=8,851*		
	FEV_1 (ml)	FVC (ml)	FEV_1/FVC (%)	FEV_1 (ml)	FVC (ml)	FEV_1/FVC (%)
TT	**38.08**	**58.32**	-0.13	1.60	1.76	0.00
	(22.65 to 53.51)	**(40.09 to 76.56)**	(-0.30 to 0.04)	(-6.80 to 10.00)	(-8.44 to 11.99)	(-0.11 to 0.11)
FAI	**-17.24**	**-27.65**	0.09	**-10.39**	**-14.41**	0.01
	(-30.62 to -3.85)	**(-43.48 to -11.83)**	(-0.05 to 0.24)	**(-16.88 to -3.90)**	**(-22.30 to -6.52)**	(-0.07 to 0.10)
cFT	2.37	4.76	-0.03	**-9.88**	**-13.66**	0.01
	(-11.85 to 16.59)	(-12.05 to 21.57)	(-0.18 to 0.13)	**(-18.01 to -1.76)**	**(-23.55 to -3.78)**	(-0.10 to 0.11)
SHBG	**50.35**	**77.09**	-0.17	**19.43**	**32.44**	**-0.15**
	(34.58 to 66.12)	**(58.47 to 95.71)**	(-0.34 to 0.00)	**(8.97 to 29.89)**	**(19.73 to 45.15)**	**(-0.28 to -0.01)**

Linear regression model adjusted for age, age^2, standing height, BMI, smoking status, pack years, Townsend deprivation score, days per week of moderate physical activity, fresh fruit intake and time of appointment. TT: total testosterone. FAI: free androgen index. cFT: calculated free testosterone. SHBG: sex hormone binding globulin. *numbers of participants with no covariates missing for the adjusted model. All results are expressed in millilitres (ml) for average changes in FEV_1 and FVC levels and as percentages (%) for the FEV_1/FVC ratio, with corresponding 95% confidence intervals.

Suppl. table S2: Difference in FEV1 and FVC (ml) and FEV1/FVC (%) at baseline in men and women per sex-specific interquartile range increase (95% CI) in hormone measure. All participants with hormonal biomarker measurements and spirometry (high quality or not) available at baseline.

Hormonal measure	**Men** N=13,890*			**Women** N=12,749*		
	FEV_1 (ml)	FVC (ml)	FEV_1/FVC (%)	FEV_1 (ml)	FVC (ml)	FEV_1/FVC (%)
TT	**44.99**	**71.60**	**-0.16**	4.00	2.04	0.07
	(31.41 to 58.56)	**(54.24 to 88.97)**	**(-0.30 to -0.02)**	(-3.70 to 11.69)	(-8.79 to 12.86)	(-0.04 to 0.18)
FAI	**-20.49**	**-29.13**	0.04	**-8.40**	**-13.10**	0.04
	(-31.51 to -9.48)	**(-43.23 to -15.02)**	(-0.08 to 0.15)	**(-14.19 to -2.61)**	**(-21.24 to -4.96)**	(-0.04 to 0.12)
cFT	0.91	4.70	-0.05	**-9.12**	**-14.49**	0.06
	(-11.77 to 13.59)	(-11.53 to 20.93)	(-0.18 to 0.08)	**(-16.46 to -1.78)**	**(-24.81 to -4.16)**	(-0.04 to 0.16)
SHBG	**58.81**	**93.51**	**-0.22**	**20.28**	**27.62**	-0.04
	(44.94 to 72.68)	**(75.79 to 111.24)**	**(-0.37 to -0.08)**	**(10.94 to 29.62)**	**(14.48 to 40.76)**	(-0.17 to 0.09)

Linear regression model adjusted for age, age^2, standing height, weight, smoking status, pack years, Townsend deprivation score, days per week of moderate physical activity, fresh fruit intake and time of appointment. TT: total testosterone. FAI: free androgen index. cFT: calculated free testosterone. SHBG: sex hormone binding globulin. *numbers of participants with no covariates missing for the adjusted model. All results are expressed in millilitres (ml) for average changes in FEV_1 and FVC levels and as percentages (%) for the FEV_1/FVC ratio, with corresponding 95% confidence intervals.

Suppl. table S3: Difference in decline between baseline and 2nd follow-up in FEV_1 and FVC (ml/yr) and FEV_1/FVC (%/yr) in men and women per sex-specific interquartile range increase in hormone level measured at baseline. All participants with hormonal biomarker measurements and spirometry (high quality or not) available at baseline and follow-up.

Hormonal measure	**Men** N=10,302*			**Women** N=9,621*		
	FEV_1	FVC	FEV_1/FVC	FEV_1	FVC	FEV_1/FVC
TT	**-2.72**	-2.40	**-0.02**	0.30	0.35	-0.00
	(-4.19 to -1.24)	(-4.98 to 0.18)	**(-0.04 to -0.00)**	(-0.65 to 1.24)	(-2.10 to 2.80)	(-0.02 to 0.02)
FAI	**1.55**	1.32	**0.02**	0.61	-0.25	0.01
	(0.43 to 2.67)	(-0.64 to 3.28)	**(0.00 to 0.03)**	(-0.06 to 1.27)	(-1.96 to 1.46)	(-0.00 to 0.02)
cFT	0.71	0.80	0.01	0.81	-0.10	0.01
	(-0.65 to 2.07)	(-1.57 to 3.18)	(-0.01 to 0.03)	(-0.03 to 1.65)	(-2.28 to 2.09)	(-0.01 to 0.02)
SHBG	**-4.67**	**-4.44**	**-0.04**	-0.98	1.42	-0.02
	(-6.11 to -3.22)	**(-6.97 to -1.91)**	**(-0.06 to -0.02)**	(-2.03 to 0.07)	(-1.32 to 4.16)	(-0.04 to 0.00)

Linear mixed model regression model adjusted for age, age^2, standing height, BMI, smoking status, pack years, Townsend deprivation score, days per week of moderate physical activity, fresh fruit intake and time of appointment. TT: total testosterone. FAI: free androgen index. cFT: calculated free testosterone. SHBG: sex hormone binding globulin. *numbers of participants with no covariates missing for the adjusted model. All results are expressed in millilitres per year (ml/yr) for average changes in FEV_1 and FVC decline and percentages per year (%/yr) for FEV_1/FVC ratio decline, with corresponding 95% confidence intervals.

Suppl. table S4: Difference in decline between baseline and 2nd follow-up in FEV_1 and FVC (ml/yr) and FEV_1/FVC (%/yr) in men and women per sex-specific interquartile range increase in hormone level measured at baseline. All participants with hormonal biomarker measurements and high quality spirometry available at baseline. Model adjusted for baseline lung function parameter.

Hormonal measure	**Men** N=4,333*			**Women** N=4,734*		
	FEV_1	FVC	FEV_1/FVC	FEV_1	FVC	FEV_1/FVC
TT	-1.00 (-2.63 to 0.63)	-0.51 (-2.47 to 1.46)	-0.02 (-0.03 to 0.00)	**0.97 (0.09 to 1.84)**	**1.36 (0.29 to 2.43)**	0.00 (-0.01 to 0.01)
FAI	1.22 (-0.12 to 2.55)	**1.70 (0.09 to 3.30)**	0.01 (-0.00 to 0.02)	**0.82 (0.21 to 1.42)**	**1.16 (0.42 to 1.90)**	-0.00 (-0.01 to 0.01)
cFT	0.82 (-0.64 to 2.29)	1.53 (-0.22 to 3.29)	0.00 (-0.02 to 0.02)	**1.02 (0.23 to 1.82)**	**1.55 (0.58 to 2.51)**	-0.00 (-0.01 to 0.01)
SHBG	**-3.10 (-4.73 to -1.47)**	**-3.34 (-5.30 to -1.38)**	**-0.03 (-0.04 to -0.01)**	-0.60 (-1.65 to 0.46)	-1.03 (-2.32 to 0.25)	0.00 (-0.01 to 0.02)

Linear mixed model regression model adjusted for age, age^2, standing height, BMI, smoking status, pack years, Townsend deprivation score, days per week of moderate physical activity, fresh fruit intake, time of appointment and respective lung function parameter at baseline. TT: total testosterone. FAI: free androgen index. cFT: calculated free testosterone. SHBG: sex hormone binding globulin. *numbers of participants with no covariates missing for the adjusted model. All results are expressed in millilitres per year (ml/yr) for average changes in FEV_1 and FVC decline and percentages per year (%/yr) for FEV_1/FVC ratio decline, with corresponding 95% confidence intervals.

Suppl. table S5: Difference in FEV1 and FVC (ml) and FEV1/FVC (%) at baseline in men per sex-specific interquartile range increase (95% CI) in hormone measure <u>after exclusion of men with prostate cancer or prostate hypertrophy</u>. Participants with hormonal biomarker measurements and high quality spirometry available at both time points.

Hormonal measure	**Men** N=4,530*		
	FEV_1 (ml)	FVC (ml)	FEV_1/FVC (%)
TT	**31.32**	**50.59**	-0.13
	(7.81 to 54.83)	**(23.04 to 78.14)**	(-0.39 to 0.13)
FAI	-7.59	**-23.43**	0.20
	(-27.48 to 12.29)	**(-46.75 to -0.12)**	(-0.02 to 0.42)
cFT	7.43	3.61	0.09
	(-13.55 to 28.42)	(-21.01 to 28.23)	(-0.15 to 0.32)
SHBG	**31.79**	**65.30**	**-0.34**
	(7.61 to 55.97)	**(36.99 to 93.61)**	**(-0.60 to -0.07)**

Linear regression model adjusted for age, age^2, standing height, weight, smoking status, pack years, Townsend deprivation score, days per week of moderate physical activity, fresh fruit intake and time of appointment. TT: total testosterone. FAI: free androgen index. cFT: calculated free testosterone. SHBG: sex hormone binding globulin. *numbers of participants with no covariates missing for the adjusted model. All results are expressed in millilitres (ml) for average changes in FEV_1 and FVC levels and as percentages (%) for the FEV_1/FVC ratio, with corresponding 95% confidence intervals.

Suppl. table S6: Difference in decline between baseline and 2nd follow-up in FEV_1 and FVC (ml/yr) and FEV_1/FVC (%/yr) in men per sex-specific interquartile range increase in hormone level measured at baseline, after exclusion of men with prostate cancer or prostate hypertrophy. Participants with hormonal biomarker measurements and high quality spirometry available at baseline and follow-up.

Hormonal measure	**Men** N=3,841*		
	FEV_1	FVC	FEV_1/FVC
TT	-0.76	-0.09	-0.02
	(-2.63 to 1.12)	(-2.38 to 2.20)	(-0.04 to 0.00)
FAI	**1.56**	1.74	0.02
	(0.02 to 3.09)	(-0.13 to 3.61)	(-0.00 to 0.03)
cFT	1.31	1.92	0.01
	(-0.39 to 3.01)	(-0.15 to 3.98)	(-0.01 to 0.02)
SHBG	**-2.98**	**-2.85**	**-0.03**
	(-4.82 to -1.14)	**(-5.10 to -0.61)**	**(-0.05 to -0.01)**

Linear mixed model regression model adjusted for age, age^2, standing height, BMI, smoking status, pack years, Townsend deprivation score, days per week of moderate physical activity, fresh fruit intake and time of appointment. TT: total testosterone. FAI: free androgen index. cFT: calculated free testosterone. SHBG: sex hormone binding globulin. *numbers of participants with no covariates missing for the adjusted model. All results are expressed in millilitres per year (ml/yr) for average changes in FEV_1 and FVC decline and percentages per year (%/yr) for FEV_1/FVC ratio decline, with corresponding 95% confidence intervals.

Suppl. table S7: Correlations between sex hormone indices and lung function parameter (FEV_1, FVC, FEV_1/FVC) in men and women at baseline (2006-2010) in UK Biobank.

	TT	FAI	cFT	SHBG	FEV_1	FVC	FEV_1/FVC
TT	1.000	0.176	0.680	0.565	0.082	0.112	-0.046
FAI	**0.687***	1.000	0.791	-0.605	0.128	0.087	0.110
cFT	**0.806***	**0.981***	1.000	-0.185	0.132	0.119	0.051
SHBG	**-0.039***	**-0.718***	**-0.585***	1.000	-0.054	0.003	-0.127
FEV_1	**0.068***	**-0.040***	**-0.016***	**0.118***	1.000	0.901	0.404
FVC	**0.045***	**-0.080***	**-0.053***	**0.153***	**0.930**	1.000	-0.025
FEV_1/FVC	**0.075***	**0.098***	**0.095***	**-0.071***	**0.331**	**-0.031**	1.000

TT: total testosterone. FAI: free androgen index. cFT: calculated free testosterone (according to Vermeulen, modified by Ho). SHBG: sex hormone binding globulin. Men: top triangle. Women: bottom triangle, **bold**.

Pearson's correlations were calculated for all variables in men as their distribution followed a normal distribution. This also applied for correlations between lung function parameters in women.

*Spearman's rank correlation coefficient was used for all correlations with hormonal markers in women as the distribution of hormonal markers was not normal in this group.